REMARKS

Applicants have canceled withdrawn claims 32-38, 40, and 74-86 without prejudice. Claim 39 has been amended mainly for clarification. The amendments are made solely to expedite prosecution of the application, and Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications. Claim 97 has been added. Support for the claim amendments and new claim 97 can be found throughout the specification (e.g., page 17, lines 7-21; page 20, lines 13-17; page 26, lines 10-21; page 28, lines 22-26; page 53, lines 15-25). No new matter has been introduced.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Applicants note with appreciation that the Examiner has entered the Amendment filed on May 7, 2004 in view of Applicants' previous response, as well as the Amendment filed on January 31, 2005.

Election/Restriction

The Examiner has acknowledged Applicants' election, with traverse, of Group V in the Response filed on October 3, 2003. As described above, Applicants have canceled, without prejudice, withdrawn claims 32-38, 40, and 74-86.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 39, 73, 89-90, 93, and 95-96 are rejected under 35 USC § 112, first paragraph, for alleged lack of written description. Applicants traverse these rejections to the extent it is maintained over the claims as amended.

Specifically, the Examiner has asserted that "the specification does not teach what is the complete structure of any agent. Except for disclosing that an agent or modulator could be any compound, the specification does not teach what would be the structure of a species of the genus" (Office Action, page 3, lines 22-24).

The Examiner appears to be asserting that because the agent recited in the pending claims are not disclosed in detail, the written description is deemed to be incomplete. However, what is required by the most recent version of the *Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement*, which appeared in the Federal Register in January 2001, Vol. 66, No. 4, pp. 1104-1111, is only:

> "sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., **or** by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus...." (emphasis added)

While the Examiner appears to be requiring physical and/or chemical properties, these are obviously not required by the Guidelines – the relevant structures have been disclosed, not to mention actual reduction to practice of several species within the claimed genus.

Moreover, the subject matter claimed in amended claim 39 is focused on a method of assessing an effect of an agent on arterial smooth muscle cell, not on the agent per se. One of skill in the art would understand that the structures of the agents need not to be known for the purposes of assessing their biological effects. Indeed, most of the experiments were performed in large scale screening assays involving use of compounds present in a library where the structures of the compounds were not necessarily known at the time of the experiments. In particular, the specification teaches on page 25, lines 3-23:

> Test agents to be assessed for their effects on arterial cells (e.g., arterial endothelial cells, arterial smooth muscle cells) or venous cell (e.g., venous endothelial cells, venous smooth muscle cells) can be any chemical agent (e.g., element, molecule, compound) which is made synthetically, made by recombinant techniques or isolated from a natural source. For example, test agents can be peptides, polypeptides, peptoids, peptidomimetics, sugars, hormones, or nucleic acid molecules (including both single-stranded and double-stranded DNA, RNA or antisense nucleic acid molecules). In addition, test agents can be small molecules or molecules of greater complexity made by combinatorial chemistry, for example, and compiled into libraries. These libraries can comprise, for example, alcohols, alkyl halides, amines, amides, esters, aldehydes, ethers and other classes of organic compounds. Test agents can also be natural or genetically-engineered products isolated from lysates or growth media of cells (e.g., bacterial, animal or plant) or the cell lysates or growth media themselves. Presentation of test compounds to the test system can be in either an isolated form or as mixtures of compounds, especially in initial screening steps.

In addition, the specification provides certain specific agents which bind Ephrin B2, for example, "an antibody or antigen-binding fragment which binds Ephrin B2 and a soluble Ephrin B2 binding portion of EphB4" (see, e.g., page 19, lines 18-20; page 7, lines 22-23;).

In view of the teachings of the specification and the knowledge in the art at the time the application was filed, a skilled artisan would appreciate that a variety of test agents can be used in the claimed methods. Under the Guidelines for the Examination of Patent Applications Under the Written Description Requirement, 66 Fed. Reg. 1104, 1105 (Jan. 5, 2001), "[i]nformation which is well known in the art need not be described in detail in the specification."

Further, the Examiner repeats the assertion that "the claims recite any member of Ephrin or Eph family, however, the specification only teaches EphrinB2 and EphB4 . . . Neither the specification nor the art of record teaches any other Ephrin or Eph proteins expressed by arterial smooth muscle cells. In other words, there is no evidence of record that the applicants had possession of any other arterial smooth muscle cells that expressed any other Ephrin or Eph than EphrinB2 and EphB4" (Office Action, page 4, lines 3-9).

Applicants respectfully remind the Examiner that Applicants have amended independent claim 39 in the previous response to define the Ephrin family ligand to be Ephrin B2 and to remove the recitation of "Eph family receptor." Accordingly, the claims as amended do not recite any member of Ephrin or Eph family, contrary to the Examiner's assertion. Clarification is respectfully requested.

In sum, Applicants submit that the Examiner's rejection is unfounded, both because the alleged grounds bear no relation to the written description requirement and because any failure to disclose purification details is nothing more than the omission of routine details that would be clear to a skilled artisan undertaking the purification process. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 39, 73, 89-90, 93, and 95-96 are rejected for lack of enablement. Applicants respectfully traverse these rejections to the extent it is maintained over the claims as amended.

In particular, the Examiner asserts that "the amendment to recite 'wherein said agent binds Ephrin B2' is considered new matter . . . there is no teaching that the compounds made must be constructed such that they bind anything, to the contrary it appears that any agent can be tested" (Office Action, the paragraph bridging pages 4 and 5).

As described above, Applicants have amended independent claim 39 by removing the recitation "wherein said agent binds Ephrin B2," thereby rendering the rejection moot. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 39, 73, 89-90, 93, and 95-96 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Specifically, the Office Action asserts that "the claims are unclear because the antecedent basis for the wherein clause indicating that the agent binds to a cell-surface protein is not sufficiently set forth in the claims" (Office Action, page 6, lines 14-15).

As described above, Applicants have amended independent claim 39 by removing the recitation "wherein said agent binds Ephrin B2," thereby rendering the rejection moot. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim Rejections under 35 U.S.C. § 102

Applicants note with appreciation that the Examiner has withdrawn the rejections under 35 U.S.C. § 102(b) and under 35 U.S.C. § 102(e) in view of Applicants' Amendment and arguments filed on January 31, 2005.

Further, Applicants submit that the claims as amended are not anticipated by any of the previously cited prior art. Independent claim 39 as amended recites a method for assessing an effect of an agent on arterial smooth muscle cells, comprising: a) adding said agent to arterial smooth muscle cells expressing Ephrin B2; and b) comparing the effect of said agent on said arterial smooth muscle cells with a suitable control, wherein comparing the effect comprises: (i)

measuring Ephrin B2 gene expression; (ii) detecting Ephrin B2 binding to an EphB4 receptor; or (iii) measuring Ephrin B2 activation or inhibition (emphasis added).

To anticipate an invention, the prior art reference must disclose each and every aspect of the claimed invention. Applicants note that the cited references (Yamamoto et al., Haber et al., and Olson et al.) merely describe treating cultured arterial smooth muscle cells with different compounds. However, none of these references teach or suggest that comparing the effect comprises: (i) measuring Ephrin B2 gene expression; (ii) detecting Ephrin B2 binding to an EphB4 receptor; or (iii) measuring Ephrin B2 activation or inhibition. In fact, these references are totally silent on the role of Ephrin in smooth muscle cells. Dependent claims 73, 89-90, 93, and 95-96 are not anticipated by any of the cited references for the same reasons described as above.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945, under Order No. CTCH-P01-007.**

Dated: July 29, 2005

Respectfully submitted,

By _____

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